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COMPOUND NUMBER: PF-04171327

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT00938587

PROTOCOL NO.: A9391005

PROTOCOL TITLE: A Phase 2a, Randomized, Double-Blind, Active and Placebo-Controlled Study of PF-04171327 in the Treatment of the Signs and Symptoms of Rheumatoid Arthritis

Study Centers: 29 centers (5 centers in the Czech Republic, 1 center in Hong Kong, 4 centers in Hungary, 3 centers in the Russian Federation, 2 centers in Serbia, 1 center in Singapore, 1 center in Slovakia, 2 centers in Spain, 1 center in Turkey, 4 centers in the Ukraine, and 5 centers in the United States). An additional 23 centers were shipped study drug but did not enroll any subjects.

Study Initiation Date and Primary Completion or Completion Dates: 07 October 2009 to 29 July 2010.

Phase of Development: Phase 2a

Study Objectives: The primary objective was to determine the efficacy of PF-04171327 (high and low dose) compared to placebo as assessed by the Disease Activity Score using 28 joint counts C-reactive protein (DAS28-4 [CRP]) at Week 2. Secondary objectives were: 1) to determine the efficacy of prednisone 5 mg compared to placebo as assessed by DAS28-4 (CRP) at Week 2; 2) to assess the safety and tolerability of PF-04171327 and prednisone 5 mg when administered to rheumatoid arthritis (RA) subjects for 2 weeks; 3) to evaluate PF-00251802 pharmacokinetics (PK) and biomarker responses in RA subjects; and 4) to evaluate the PK of methotrexate (MTX) in the presence of PF-00251802.

METHODS

Study Design: This was a Phase 2a, international, multi-center, 2-week, randomized, double-blind, parallel-group, active- and placebo-controlled proof of concept study in subjects with RA. Subjects were randomized in a 1:1:1:1 ratio such that 20 subjects received either PF-04171327 10 mg or 25 mg tablets, prednisone 5 mg, or placebo every day (QD) while on background MTX. Subjects were screened for participation within 1 month prior to administration of the study medication. Subjects' participation was approximately 70 days with at least 5 clinic visits. Active disease was required in the study and was defined as 6 or

more tender/painful joints and 6 or more swollen joints out of a standard 28-joint assessment, and a CRP of 0.7 mg/dL or higher. The primary endpoint was DAS28-4 (CRP) at Week 2. Secondary endpoints included tender/painful and swollen joint count (SJC; using 28 joint counts), CRP, Health Assessment Questionnaire – Disability Index (HAQ-DI), Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician Global Assessment of Arthritis, and Short-form Health Survey with 36 Questions (SF-36) version 2 (SF-36v2). Subjects were assessed for safety (adverse events [AEs], clinical laboratory assessments, body weight, vital signs and 12-lead electrocardiograms [ECGs], PK (apparent oral clearance (CL/F) of MTX prior to PF-04171327 dosing and in the presence of PF-00251802 on Day 14 characterized and compared statistically using a population PK (model fitted to the MTX PK data) and pharmacodynamics (PD, biomarker assessment [circulating lymphocyte, neutrophils and eosinophil counts, osteocalcin, plasma cortisol, urinary N terminal telopeptide of type 1 collagen {uNTX-1}, and adiponectin]).

Number of Subjects (Planned and Analyzed): A total of 20 subjects/arm (80 subjects) was planned; 86 subjects were analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were 18 years of age or older with RA (minimum duration of 3 months); diagnosis of RA fulfilled 4 out of 7 criteria established by the American College of Rheumatology for diagnosis of RA. Subjects had a minimum disease activity of at least 6 or more swollen joints and 6 or more tender joints at the Screening (or Baseline) visits and CRP of 0.7 mg/dL or higher (≥7.0 mg/L) at the Screening visit.

Study Treatment: PF-04171327 5 mg and 10 mg tablets, prednisone 5 mg, or placebo for PF-04171327 and prednisone (depending on treatment allocation) were provided by the sponsor in bulk supply. Subjects used their own MTX supplies during the 2-week study.

Efficacy Evaluations:

Tender/Painful and Swollen Joint Counts: Assessed at the Screening visit, and prior to dosing at Baseline, Week 1, Week 2 (or early withdrawal [EW]), and at the Follow-up visit (Day 42 ± 3 days).

C-Reactive Protein: Blood for CRP evaluations collected at the Screening visit, and prior to dosing at Baseline, Week 1, Week 2 (or EW), and at the Follow-up visit (Day 42 ± 3 days).

Patient's Assessment of Arthritic Pain: Subjects were asked to rate how much arthritic pain they were having prior to dosing at Baseline, Week 1, and Week 2 (or EW).

Patient's Global Assessment of Arthritis: Subjects completed the global assessment of arthritis prior to dosing at Baseline, Week 1, and Week 2 (or EW).

Physician Global Assessment of Arthritis: Investigators completed the global assessment of arthritis prior to dosing at Baseline, Week 1, and Week 2 (or EW).

Health Assessment Questionnaire–Disability Index: Subjects were asked to complete the HAQ-DI prior to dosing at Baseline, Week 1, and Week 2 (or EW).

SF-36v2: Health status was measured using the self-administered SF-36v2 questionnaire prior to any procedures being performed at Baseline and Week 2 (or EW).

DAS Assessments: The components of the DAS28 arthritis assessment were tender/painful joint count (28), SJC (28), CRP, and Patient's Global Assessment of Arthritis (included in DAS28-4 only).

American College of Rheumatology (ACR) Assessments: ACR20, ACR50, and ACR70 (20%, 50%, or 70% improvement in tender and SJCs and 20%, 50%, 70% improvement in 3 of the 5 remaining ACR-core set measures, respectively: patient and physician global assessments, pain, disability, and an acute-phase reactant) assessed at every visit (Baseline, Week 1, Week 2 [or EW].

Pharmacokinetic and Pharmacodynamic Evaluations: PK assessments are reported in a separate report. Pharmacodynamic (PD) assessments included the following biomarkers:

Plasma for Analysis of Osteocalcin: Samples collected at Hours 0, 1, 2, 3, and 4 at Baseline, Week 1, and 2 (or EW), and at the Follow-up visit.

Urine for Analysis of NTX-1/urinary creatinine (uCr): Urine samples for the bone resorption marker type I collagen NTX-1/uCr were collected at Hour 0 at Baseline and at Weeks 1 and 2 (or EW).

Plasma for Analysis of Cortisol: Blood samples for cortisol analysis were collected at Hours 0, 1, 2, 3, and 4 at Baseline, Week 1, and 2 (or EW), and at the Follow-up visit.

Serum for Analysis of Adiponectin: Blood samples for adiponectin analysis were collected at Hour 0 at Baseline, Week 1, and Week 2 (or EW).

Safety Evaluations: Safety evaluations included AEs, clinical laboratory tests, body weight, vital signs (blood pressure, heart rate, and temperature), and 12-lead ECGs.

Statistical Methods: The sample size for the study was based on the change from baseline on DAS28-4 (CRP). A sample size of 20 subjects per arm provided 90% power to detect a standardized difference of 1.0 between any active and placebo treatment using a one-sided test. The per comparison type I error rate is maintained at 5% level. The full analysis set (FAS) included all randomized subjects who received at least 1 dose of the randomized investigational drug. The primary analysis population for this study is defined by the FAS set of subjects.

Primary Analysis: The primary analysis was performed on the DAS28-4 (CRP) change from baseline using a mixed-model repeated measures (MMRM) analysis. The primary comparison was the contrast of either dose of PF-04171327 versus placebo at Week 2.

Categorical variables (ACR20/50/70) were analyzed using Barnard's exact test. Continuous variables (DAS28, ACR components, etc) were analyzed using the MMRM model with treatment group, time and treatment-by-time interaction as fixed effects, subject as random effect, and baseline as the covariate. Compound symmetry was used for within-subject

correlation structure across measurements over time. In case of non-convergence of the MMRM model, the analysis of covariance (ANCOVA) model with treatment as fixed effect and baseline as covariate were fitted by week.

Secondary Analysis: Secondary endpoints were analyzed by either categorical or continuous methods.

PK of PF-00251802 following administration of PF-04171327 tablets were characterized using a population PK approach. The MTX PK data were also described using mixed-effects models, and differences in MTX CL/F with or without co-administration of PF-04171327 (expressed as the ratio of CL/F on Day 1 and Day 14) were assessed as part of the PK model. Mixed-effects modeling was implemented in NONMEM v 6.2.

PD effects of PF-04171327, prednisolone, and placebo were assessed by the following biomarkers: circulating lymphocyte, neutrophil, and eosinophil counts, and cortisol, osteocalcin, urinary NTX-1/uCr, and adiponectin concentrations. The PD data were summarized by day and time for each treatment group. In addition, area under the effect curve from 0 to 4 hours ($AUEC_{[0\text{-}4\ hour]}$) postdose was calculated for cortisol and osteocalcin, and neutrophil, eosinophil, and lymphocyte counts. The values for the PF-04171327 and prednisone treatment groups were compared to placebo, and the PF-04171327 groups were also compared to 5 mg prednisone using an analysis of variance (ANOVA) model.

RESULTS

Subject Disposition and Demography: Of the 208 subjects screened, 86 were randomized and received study treatment. A total of 7 subjects were discontinued from the study (Table 1). Of these subjects, 79 (92%) completed the study (86% to 96% across groups).

Table 1. Subject Evaluation Groups

	PF-04171327			
	10 mg	**25 mg**	**Prednisone 5 mg**	**Placebo**
Number of subjects				
Screened N=208				
Assigned to study treatment	21	22	21	22
Treated	21	22	21	22
Completed	18	21	20	20
Discontinued	3	1	1	2
Analyzed for pharmacokinetics				
PK parameter	21	22	21	0
PK concentration	21	22	21	0
Analyzed for safety				
Adverse events	21	22	21	22
Laboratory data	21	22	21	22
Vital signs	21	22	21	22
Electrocardiogram	21	22	21	22

Abbreviations: N = number of subjects in study population

Subjects were between the ages of 29 and 77 years with mean ages ranging from 53.8 to 56.5 years across groups. The majority of subjects in each group were female (54.5% to 90.9% across groups), and hormone status was primarily postmenopausal (58.3% to 80.0% across groups). The majority of subjects were white (from 90% to 100% across groups).

The mean duration of RA ranged from 7.61 years to 9.27 years. DAS28 (CRP), SJC, and TJCs were generally similar across the groups at baseline. HAQ-DI scores were higher in the PF-04171327 10 mg (1.62) and placebo groups (1.63) than in the PF-04171327 25 mg (1.47) and prednisone 5 mg groups (1.46). CRP was lowest in the placebo group (13.1 mg/L). The mean baseline MTX dose across groups varied from 12.61 mg to 13.18 mg per week.

Efficacy Results: Primary: Table 2 presents a summary of the statistical analysis for the change from baseline in DAS28-4 (CRP) at Weeks 1 and 2. There was greater improvement in DAS28-4 (CRP) for the PF-04171327 treated groups compared with placebo. At Week 2, PF-04171327 10 mg and PF-04171327 25 mg showed a statistically significantly greater improvement in the adjusted mean change from baseline in DAS28-4 (CRP) over placebo by -0.73 ($p=0.0141$) and -1.26 ($p<0.0001$), respectively, based on the MMRM analysis. PF-04171327 25 mg also showed a statistically significantly greater improvement in the adjusted mean change from baseline in DAS28-4 (CRP) over prednisone by -1.06 ($p=0.0004$). Prednisone did not show statistically significant differences in the adjusted mean change from baseline in DAS28-4 (CRP) over placebo. At Week 1, a similar trend was observed with respect to statistically significant changes in the adjusted mean change from baseline in DAS28-4 (CRP) scores for the PF-04171327 treated groups vs placebo and prednisone.

Table 2. Summary of Statistical Analysis (MMRM): Change from Baseline for DAS28-4 (CRP) at Weeks 1 and 2 - Full Analysis Set

		PF-04171327			
Visit	**Statistic**	**10 mg N=21**	**25 mg N=22**	**Prednisone 5mg N=21**	**Placebo N=22**
Baseline					
	Mean (SD) *Median* *Min, Max* *n*	6.04 (0.869) 6.31 4.60, 7.69 21	6.14 (0.755) 6.14 4.87, 7.98 22	5.92 (0.658) 5.84 4.60, 7.07 21	6.03 (0.810) 6.06 4.50, 7.34 22
Change from Baseline at Week 1					
	LSM (SE) *n*	-1.19 (0.207) 20	-1.63 (0.202) 21	-0.70 (0.202) 21	-0.54 (0.199) 21
	Versus Prednisone *LSMD [90% CI]* *p-value versus prednisone*	-0.49 [-0.97, -0.01] 0.0956	-0.93 [-1.40, -0.45] 0.0016	--	--
	Versus Placebo *LSMD [90% CI]* *p-value versus placebo*	-0.65 [-1.13, -0.17] 0.0258	-1.09 [-1.56, -0.62] 0.0002	-0.16 [-0.63, 0.31] 0.5692	--
Change from Baseline at Week 2					
	LSM (SE) *n*	-1.69 (0.212) 18	-2.22 (0.202) 21	-1.17 (0.204) 20	-0.96 (0.199) 21
	Versus Prednisone *LSMD [90% CI]* *p-value versus prednisone*	-0.52 [-1.01, -0.03] 0.0811	-1.06 [-1.53, -0.58] 0.0004	--	--
	Versus Placebo *LSMD [90% CI]* *p-value versus placebo*	-0.73 [-1.21, -0.24] 0.0141	-1.26 [-1.73, -0.79] <0.0001	-0.21 [-0.68, 0.27] 0.4711	--

Baseline was Day 1 predose measure.
MMRM with model terms: treatment, time, treatment-by-time interaction as fixed effects, subjects as random effect, baseline as the covariate and CS as covariance structure.
Abbreviations: CI = confidence interval, CRP = C-reactive protein, CS = compound symmetry, DAS28-4 = Disease Activity Score using 28 joint counts C reactive protein, LSM = least square mean, LSMD = least square mean difference, max = maximum, min = minimum, MMRM = mixed-model repeated measures, n = number of subjects within a specific category, N = number of subjects in study population, SD = standard deviation, SE = standard error

At the Follow-up visit (Day 42 ± 3 days) 3 individual components (tender joint counts [TJCs], SJCs, and CRP) of the DAS28-4 were also assessed. For SJCs, PF-04171327 10 mg showed greater improvement in the adjusted mean change from baseline over prednisone by 3.58 (p=0.0023). Levels of CRP increased in all groups and were higher in the PF-04171327 10 mg group compared with placebo (p=0.0155) and prednisone 5 mg (p=0.0127). There were no meaningful differences between the PF-04171327 dose groups and placebo and the PF-04171327 dose groups and prednisone 5 mg in the change from baseline in TJCs at Week 6 (p>0.05).

Secondary: ACR20/50/70 Response: PF-04171327 25 mg had significantly higher responses than placebo for all 3 assessments (ACR20/50/70) and significantly higher responses than prednisone 5 mg for the ACR50/70 assessments.

Tender Joint Counts: There were no meaningful differences between the PF-04171327 dose groups and placebo or the PF-04171327 dose groups and prednisone 5 mg in the change from baseline in TJCs at Weeks 1 and 2. At Week 2, the percent change from baseline in median

TJCs was -55%, -50%, -40%, and -44% for the PF-04171327 10 mg, PF-04171327 25 mg, prednisone 5 mg, and placebo groups, respectively.

Swollen Joint Counts: At Week 2, the percent change from baseline in median SJCs was -44%, -60%, -53%, and -56% for the PF-04171327 10 mg, PF-04171327 25 mg, prednisone 5 mg, and placebo groups, respectively.

CRP: The percent change from baseline in median CRP at Week 2 was -80%, -89%, -41%, and 0% for the PF-04171327 10 mg, PF-04171327 25 mg, prednisone 5 mg, and placebo groups, respectively.

Both PF-04171327 dose groups had clinically and statistically significant reductions in CRP at Weeks 1 and 2 (Week 1, adjusted mean change from baseline -12.63 mg/L [p=0.0053] and -17.44 mg/L [p=0.0001] for PF-04171327 10 mg and 25 mg, respectively; Week 2, adjusted mean change from baseline -13.51 mg/L [p=0.0037] and -14.93 mg/L [p=0.0009] for PF-04171327 10 mg and 25 mg, respectively). The change from baseline in median CRP for both PF-04171327 dose groups was also clinically and statistically significant compared with prednisone 5 mg (Week 1, adjusted mean change from baseline -8.47 mg/L [p≥0.05] and -13.29 mg/L [p=0.0030] for PF-04171327 10 mg and 25 mg, respectively; Week 2, adjusted mean change from baseline -9.68 mg/L [p=0.0389] and -11.10 mg/L [p=0.0142] for PF-04171327 10 mg and 25 mg, respectively). At Weeks 1 and 2, the change from baseline in median CRP for prednisone 5 mg was higher than placebo but these differences were not clinically or statistically significant.

Patient's Assessment of Arthritis Pain: At Week 2, PF-04171327 10 mg and 25 mg showed greater improvement in arthritis pain over placebo (adjusted mean change from baseline in subject's assessment of arthritis pain over placebo by -11.62 [p>0.05] and -15.89 [p=0.0271], respectively) based on the MMRM analysis. Greater improvement in arthritis pain over placebo was noted at Week 1 for both PF-04171327 dose groups (adjusted mean change from baseline in subject's assessment of arthritis pain over placebo by -2.84 and -8.72 for the PF-04171327 10 mg and 25 mg groups, respectively [p>0.05]). There were no meaningful differences between the PF-04171327 dose groups and the prednisone 5 mg group nor between the prednisone 5 mg group and placebo group in subject's assessment of arthritis pain.

Physician Global Assessment of Arthritis: At Week 2, PF-04171327 10 mg and 25 mg showed greater improvement in the physician's global assessment of arthritis over placebo (adjusted mean change from baseline in physician's global assessment of arthritis over placebo by -6.49 [p>0.05] and -17.00 [p=0.0018], respectively) based on the MMRM analysis. There were no meaningful differences between the PF-04171327 dose groups and the prednisone 5 mg group nor between the prednisone 5 mg group and placebo group in physician's global assessment of arthritis.

Patient's Global Assessment of Arthritis: At Week 2, PF-04171327 10 mg and 25 mg showed greater improvement in the subject's global assessment of arthritis over placebo (adjusted mean change from baseline in patient's global assessment of arthritis over placebo by -11.63 [p>0.05] and -17.53 [p=0.0138]), respectively, based on the MMRM analysis. There were no meaningful differences between the PF-04171327 dose groups and the prednisone 5 mg group nor between the prednisone 5 mg group and placebo group in subject's global assessment of arthritis.

HAQ: PF-04171327 10 mg and 25 mg showed greater improvement in HAQ-DI compared with placebo at Week 1 (adjusted mean change from baseline in HAQ-DI over placebo by -0.13 [p>0.05] and -0.28 [p=0.0415]) and Week 2 (adjusted mean change from baseline in HAQ-DI over placebo by -0.16 [p>0.05] and -0.44 [p=0.0013]). PF-04171327 10 mg and 25 mg also showed greater improvement in HAQ-DI compared with prednisone 5 mg at Week 1 (adjusted mean change from baseline in HAQ-DI over prednisone 5 mg by -0.16 [p>0.05] and -0.30 [p=0.0270]) and Week 2 (adjusted mean change from baseline in HAQ-DI over prednisone 5 mg by -0.05 [p>0.05] and -0.33 [p=0.0171]). There were no meaningful differences between the prednisone 5 mg group and placebo group in HAQ-DI. There were no meaningful differences between the PF-04171327 10 mg and placebo group and PF-04171327 10 mg and prednisone 5 mg group in HAQ-DI.

SF-36v2 Domain Scores: There were no significant differences between groups in the physical function domain scores. The only domain that showed a significant difference between the PF-04171327 25 mg group and placebo group was in bodily pain. At Week 2, PF-04171327 25 mg showed a significantly greater improvement in the adjusted mean change from baseline in bodily pain over placebo by 6.79 (p=0.0190). At Week 2, the mental component scores increased in all groups with changes generally similar between treatment groups.

DAS28-3 (CRP): DAS28-3 (CRP) findings were generally similar to the findings with DAS28-4 (CRP).

Pharmacokinetic and Pharmacodynamic Results:

Plasma for Analysis of PF-00251802 and Prednisolone PK:

PF-00251802 PK was characterized using a 2-compartment linear model with first-order elimination and first-order absorption with dose dependency. PF-00251802 volumes of distribution of central and peripheral compartments, and distribution clearance were fixed to the values in the previously developed model in healthy subjects, since information to estimate these parameters was limited by the sparse PK sampling in this study. Mean (SE) PF-00251802 oral clearance (CL/F) in RA subjects was estimated to be 4.74 (0.22) L/hour, which is lower than that in healthy subjects (5.98 L/hour estimated in A9391002). Therefore, overall exposure of PF-00251802 in RA subjects in this study was approximately 26% higher than that expected in healthy subjects at similar doses. Mean CL/F values were similar for the PF-04171327 10 mg and 25 mg dose groups, indicating dose-proportional increase in PF-00251802 exposure, consistent with observations in healthy subjects. The rate of PF-00251802 absorption decreased with the increase of dose, and coefficient on the power

model was estimated to be -0.342. The estimated mean terminal half-life of 35 hours in RA subjects in this study was longer than that observed previously in healthy subjects (approximately 24 hours at similar doses).

Total prednisolone PK was characterized using a sum of linear and nonlinear protein binding with free prednisolone concentration described by a 1-compartment model with first-order elimination and first-order absorption. Due to limited PK sample points, prednisolone first-order absorption rate constant, volume of distribution, and parameters for albumin and transcortin-protein binding were fixed to those reported in the literature. Mean (SE) free prednisolone oral clearance (CL/F) was estimated to be 33.8 (5.91) L/hour, which is lower than that in healthy subjects (63.9 L/hour, estimated in A9391002). The estimated apparent half-life of around 4.8 hours in RA subjects in this study was longer than that in healthy subjects (2 to 3 hours).

Plasma for Analysis of Methotrexate:

MTX AUC(0-4h) values were calculated on Day 1 (MTX alone) and Day 14 (MTX + study treatment) from MTX concentration-time profiles for 69 subjects that had MTX concentrations available up to 4 hours postdose on both occasions. The observed mean (%CV) ratios of MTX AUC(0-4h) on Day 14 and Day 1($AUC(0\text{-}4h)_{Day14}/AUC(0\text{-}4h)_{Day1}$) for the PF-04171327 10 mg, PF-04171327 25 mg, prednisone 5 mg, and placebo groups were 1.20 (40.8), 0.95 (25.3), 1.14 (58.8), and 0.91 (39.6), respectively. Median $AUC(0\text{-}4h)_{Day14}/AUC(0\text{-}4h)_{Day1}$ ratios were 1.12, 0.98, 1.14, and 0.91, respectively, for the PF-04171327 10 mg, PF-04171327 25 mg, prednisone 5 mg, and placebo groups. Mean observed MTX concentration-time profiles from 0 to 4 hours postdose were similar between Day 1 and Day 14 for all treatment groups.

A mixed-effects PK model was fitted to the MTX concentration-time data and the ratio of MTX CL/F on Day 1 (prior to dosing PF-04171327) and Day 14 (co-administration with PF-04171327) was estimated for each of the 4 treatment groups as part of the PK model. MTX concentration data from a total of 85 subjects were included in the analysis and 71 of these subjects had at least one concentration value on both Day 1 and Day 14. A 2-compartment linear model showed slight statistical improvement over a 1-compartment model (change in MOF=6.6), but was not as well-conditioned as the 1-compartment model. Therefore, parameter estimates from both models were evaluated.

Mean (90% CI) estimated $CL/F_{Day1}/CL/F_{Day14}$ ratios for the PF-04171327 25 mg treatment group were 0.92 (0.64, 1.11) from the 2-compartment model, and 0.98 (0.88, 1.08) from the 1-compartment model, consistent with the observed $AUC(0\text{-}4h)_{Day14}/AUC(0\text{-}4h)_{Day1}$ ratio estimates. These data indicated that there was no evidence of an effect of PF-04171327 25 mg on MTX pharmacokinetics in RA subjects. Mean (90% CI) estimated $CL/F_{Day1}/CL/F_{Day14}$ ratios for the PF-04171327 10 mg treatment group were 1.49 (1.10, 4.96) from the 2-compartment model and 1.24 (1.07, 1.49) from the 1-compartment model, indicating a small but statistically significant increase in MTX exposure (AUC) on Day 14 following co-administration with PF-04171327 10 mg. The estimated increase of 24% in MTX AUC from the 1-compartment model was closer to the observed

$AUC(0\text{-}4h)_{Day14}/AUC(0\text{-}4h)_{Day1}$ ratio than the increase of 49% estimated from the 2-compartment model.

Pharmacodynamics: Responses on biomarkers of glucocorticoid PD activity were not significantly different between PF-04171327 doses and prednisone 5 mg except for lymphocytes and cortisol. While both prednisone 5 mg and PF-04171327 led to suppression of plasma cortisol, both doses of PF-04171327 led to greater and maximal suppression. The increase in circulating lymphocytes was also greater with both doses of PF-04171327 than with prednisone 5 mg. Finally, although a reduction in fasting glucose occurred with both prednisone and PF-04171327, the decrease was greater with PF-04171327.

Based on observed mean values, there was a trend for greater suppression of the bone formation marker, osteocalcin, at PF-04171327 10 and 25 mg, compared to prednisone 5 mg. In addition, a trend for greater effects of PF-04171327 10 and 25 mg, compared to prednisone 5 mg, on a bone resorption marker (uNTX) was observed. Responses of 10 and 25 mg PF-04171327 on neutrophil stimulation and eosinophil suppression were similar to that of prednisone 5 mg.

The pharmacodynamic biomarkers included in this study were considered exploratory, and the study was not designed to evaluate differences between treatment groups.

Safety Results: Table 3 summarizes the treatment-emergent AEs (TEAEs) occurring in 2 or more subjects from the PF-04171327 groups.

Table 3. All Causality Treatment-Emergent Adverse Events (Treatment Related in Parenthesis) Occurring in 2 or More Subjects from the PF-04171327 Groups

MedDRA Preferred Term	PF-04171327		Prednisone 5 mg	Placebo
	10 mg N=21	25 mg N=22	N=21	N=22
Oedema peripheral	1 (0)	1 (1)	0 (0)	1 (1)
Upper respiratory tract infection	2 (1)	0 (0)	0 (0)	0 (0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities Version 13.0, N = number of subjects in study population

Table 4 summarizes the TEAEs leading to discontinuation.

Table 4. Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Treatment and/or Study

MedDRA Preferred Term	Adverse Event Start Day/Stop Day	Severity	Outcome	Causality	SAE?
PF-04171327 10 mg					
Vomiting	3/5	Moderate	Resolved	Disease under study	No
Asthenia	13/26	Severe	Resolved	Study drug	No
Placebo					
Palpitations	6/48	Mild	Resolved	Disease under study	No
Rheumatoid arthritis	3/6	Moderate	Resolved	Disease under study	No

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SAE = serious adverse event

There were no serious AEs or deaths in the study. None of the changes in safety laboratory findings, ECGs, and vital signs were considered to be of clinical concern.

CONCLUSIONS:

- PF-04171327 10 mg and 25 mg met the primary endpoint, showing significant efficacy as demonstrated by DAS28-4 (CRP) change from baseline compared to placebo at Week 2.

- Both doses of PF-04171327 showed significant decreases in DAS28-4 (CRP) as early as Week 1, and both doses were significantly better than prednisone 5 mg in reducing DAS28-4 (CRP) at Weeks 1 and 2. Similar treatment effects as compared to placebo were observed for all secondary efficacy endpoints, including ACR20/50/70, and components of the ACR such as SJC, HAQ-DI, and CRP. PF-04171327 10 mg and 25 mg reduced median CRP levels by >80% at Week 2. Prednisone 5 mg did not show significant benefit over placebo.

- The efficacy of PF-04171327 was noted to be both rapid in onset, with effects seen as early as Week 1, and dose dependent, with 25 mg demonstrating greater efficacy than 10 mg in this study.

- Although some numerical differences were noted in bone biomarker levels in subjects who received PF-04171327 compared with prednisone 5 mg, the clinical relevance of these findings is unknown.

- Both doses of PF-04171327 were associated with near-complete suppression of adrenal secretion of cortisol which necessitates close monitoring of subjects for clinical signs and symptoms of adrenal suppression.

- No clinically significant effect of PF-04171327 on MTX PK was observed. Exposures of PF-00251802 and prednisone in subjects with RA were higher than that expected in healthy subjects at similar doses.

- PF-04171327 10 mg and 25 mg and prednisone 5 mg of appeared to be well-tolerated and had an acceptable safety profile in this study.